Erythroleukaemia in the north of England: a population based study

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Abstract

***Aims*—To evaluate the incidence and outcome of acute myeloid leukaemia (AML), FAB M6 (erythroleukaemia).**

***Methods*—A demographic study in the Northern Health Region of England between 1983 and 1999.**

***Results*—Thirty three cases were diagnosed and registered prospectively. The overall incidence was 0.077 cases/100 000/year. There was a pronounced rise in incidence in patients aged 56 years or more: 6.6 times higher than that in younger patients. Overall survival was poor; median survival was 11 months for those aged less than 56 years, and three months for patients aged 56 years and above (p = 0.045). Acquired karyotypic abnormalities were found in 17 of 27 patients where analysis was attempted. When classified according to the criteria of the Medical Research Council AML trials, karyotype predicted survival, with a median overall survival of 14 months for those with "standard risk" cytogenetic results and two months for "poor risk" results (p = 0.005).**

***Conclusion*—This study demonstrates a worse survival for patients with erythroleukaemia than that reported in some published trials of selected patients.**

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Keywords: erythroleukaemia; acute myeloid leukaemia; cytogenetics; population based

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Erythroleukaemia is an unusual form of acute myeloid leukaemia (AML). Di Guglielmo first used the term in 1917. Since then, the term has been used to describe a variety of related or overlapping diseases. Dameshek introduced the term "Di Guglielmo's syndrome" in the 1950s to describe a myeloproliferative disorder characterised by erythroid hyperplasia and a rising proportion of myeloblasts, often terminating in AML.[1] Since 1975, erythroleukaemia has been used to describe one form of leukaemia included in the FAB classification of AML.[2] The diagnostic criteria were revised in 1985.[3] Cases characterised by abnormal erythroid hyperplasia but not meeting these criteria are included in other FAB subtypes of AML or myelodysplasia. Previously reported series have shown poor survival in most cases with a high incidence of karyotypic abnormalities.

The Northern Region Haematology Group serves a population of 3.1 million. It has been prospectively registering patients with AML and other haematological malignancies for over a decade, patients aged 55 years or less since 1983, and all patients since 1988.[4] We report the group's experience of erythroleukaemia.

Patients and methods

All patients diagnosed as having erythroleukaemia (M6) were included in our study. Information about age, sex, medical history, presenting features, treatment, and outcomes were collected prospectively with the cooperation of the consultant in charge of their care. Treatment was at the discretion of the supervising consultant.

DIAGNOSIS

The diagnosis of erythroleukaemia was made by inspection of Romanowsky stained bone marrow smears, with confirmation by appropriate cytochemical stains. Whenever possible this was supported by immunophenotyping of blasts. The diagnostic slides were reviewed centrally (MMR) and only cases fitting the revised FAB criteria were included. These require that at least 50% of bone marrow nucleated cells are erythroid and at least 30% of the remaining non-erythroid cells are myeloblasts.[3]

POPULATION DATA

Age specific population information was obtained from the UK 1991 census, from the Office of Population Censuses and Surveys.[5]

CYTOGENETIC ANALYSIS

The Northern Genetics Service carried out cytogenetic analysis using standard G banding techniques. A completed analysis of a normal karyotype comprised examination of 20 metaphases. Analysis was considered to have failed if less than 10 metaphases could be fully assessed unless a clonal abnormality was obvious. A clonal abnormality was defined as two or more cells showing identical chromosome gains or structural rearrangements, or three or more cells showing identical chromosome losses. A complex karyotype was defined by the presence of a clone with at least five unrelated cytogenetic abnormalities. Data from the earlier years of our study were checked retrospectively to ensure compliance with these criteria. Patients were characterised as having "standard risk" or "poor risk" cytogenetics using the criteria of the Medical Research Council (MRC) AML 12 trial.[6]

EVALUATION OF OUTCOME

Complete remission (CR) was defined as normal marrow cellularity with less than 5% blasts and near normal peripheral blood counts. For calculation of overall survival patients were

censored at the date of death or last clinic review. Event free survival (EFS) was defined as the time from diagnosis to the first event; an event was considered as death, relapse, or failure to achieve remission. Evidence of relapse was taken as the reappearance of leukaemia on a blood film or bone marrow smear. Patients who received a bone marrow transplant were censored at the time of transplant.

STATISTICAL METHODS

Survival curves were drawn according to the Kaplan–Meier method[7] and a log rank test was used to compare curves.[8]

Results

We report on 33 cases of erythroleukaemia (21 male, 12 female patients). The median age of the study population was 64 years (range, 3–84), identified from 1022 cases of AML that were registered prospectively on the regional database at the end of 1999. Since universal registration of all cases in 1988 the median age of patients with erythroleukaemia has been 60 years. Overall, the incidence was 0.077 cases/100 000 population/year, with an overall survival at five years of 6% (95% confidence interval (CI), 1% to 20%). Age standardised incidence was 0.051 cases/100 000 population/year (calculated with World standard population) and 0.078 cases/100 000 population/year (UK 1991 population).

Table 1 shows the patient characteristics.

PATIENTS AGED LESS THAN 56 YEARS

From 1983 to 1999, 12 patients (eight male, four female) aged less than 56 years were diagnosed with erythroleukaemia (median age, 39). The age specific incidence was 0.032 cases/100 000 population/year. All were anaemic at presentation, median haemoglobin (Hb) 84 g/litre (range, 49–105). The median white blood cell count (WBC) was 6.8×10^9/litre (range, 0.7–32.3). Pronounced leucocytosis was unusual. The median platelet count was 58×10^9/litre (range, 11–136).

Only one patient had a documented history of a previous haematological disorder. At the age of 30 years he had developed refractory anaemia with excess blasts in transformation (RAEB-T). This was successfully treated with FLAG chemotherapy (fludarabine, cytarabine, and granulocyte colony stimulating factor).[9] Four years later he developed erythroleukaemia. Cytogenetic analysis at that time revealed no abnormality. He was then treated with idarubicin and cytarabine, achieved CR, and proceeded to a matched unrelated donor bone marrow transplant in October 1999, and survives in remission four months later.

The other 11 patients in this age group presented as de novo leukaemia. All were treated with curative intent: three with ADE (daunorubicin, etoposide, and cytarabine) and eight with DAT (daunorubicin, tioguanine, and etoposide).[10] Only six of these 11 patients achieved CR. One patient, aged 33 years at diagnosis, underwent allogeneic bone marrow transplantation but died of toxicity related to the procedure. One patient with Down's syndrome, aged 3 years at diagnosis, remains in first CR almost five years after diagnosis following treatment with ADE. Three patients have relapsed at two, seven, and 120 months.

The patient who relapsed at 10 years was treated with DAT at diagnosis. She initially relapsed as erythroleukaemia and then as undifferentiated AML a further three, four, and five years later. Her first relapse was treated with ADE and later relapses with FLAG and then oral idarubicin and etoposide.[11] Cytogenetic analysis failed at diagnosis, but at first relapse partial deletion of chromosome 7 was found. With subsequent relapses trisomy 4 was also present. She was the only patient in this age group to have survived five years after diagnosis, but died at 191 months in fourth relapse.

Median overall survival for patients aged less than 56 years was poor at 11 months (range, 0–191), with median EFS of 4.5 months (range, 0–120). The overall survival at five years after diagnosis was 8% (95% CI, 0.2% to 15.8%). For comparison, the overall survival five years after diagnosis for the other 286 cases of AML in this age group diagnosed in our region was 38.5% (95% CI, 31% to 46%).

PATIENTS AGED 56 YEARS AND ABOVE

Twenty one patients (13 men, eight women) aged 55 years and above were diagnosed between 1988 and 1999 (median age, 69). The age specific incidence was 0.213 cases/100 000 population/year. Their blood counts at presentation were similar to the younger patients: median Hb, 74 g/litre (range, 31–114); median WBC, 5.9×10^9/litre (range, 1.1–36.1); and median platelet count, 46×10^9/litre (range, 7–163).

Three patients had a history of previous haematological disease: chronic erythroleukaemia (myelodysplasia; MDS), aplastic anaemia, and Waldenstrom's macroglobulinaemia with the subsequent development of myelodysplasia.

Only 10 of 21 patients in this group were given treatment with curative intent, four with FLAG, three with cytosine and mitoxantrone, two with DAT, and one with ADE. Three achieved CR, of whom two are alive and well in first CR 49 and 180 months after diagnosis. These patients were treated with FLAG and DAT, respectively, and both had standard risk karyotypes at diagnosis. Median survival for

Table 1 Patient characteristics

	Age less than 56 years	*Age 56 years and above*
Number	12 (8 male, 4 female)	21 (13 male, 8 female)
Median age (range)	39 years (3–53)	69 years (57–84)
Median Hb (range)	84 g/l (49–105)	74 g/l (31–114)
Median WBC (range)	6.8×10^9/l (0.7–32.3)	5.9×10^9/l (1.1–36.1)
Karyotype (classified by MRC criteria)	6 standard risk 4 poor risk 2 not done	9 standard risk 8 poor risk 4 not done
No. treated with curative intent	12	10
CR rate (95% CI)	58% (28% to 85%)	40% (12% to 74%)*
Median overall survival (range)	11 months (0–191)	3 months (0–180)*
Median event free survival (range)	4.5 months (0–120)	0 months (0–180)*
Overall 5 year survival (95% CI)	8% (0.2% to 15.8%)	5% (0.2% to 45%)*

*Patients over 55 years treated with curative intent.
CI, confidence interval; CR, complete remission; Hb, haemoglobin; MRC, Medical Research Council; WBC, white blood cell count.

Table 2 Abnormal karyotypes

Age	*Karyotype*	*Curative treatment?*	*CR?*	*Overall survival (months)*
Standard risk				
3	47,XY,+21c[4]/48,XY,+11,+21c[6]	Yes	Yes	42+
33	46,XY,del(9)(q13q22)[8]/46,XY[12]	Yes	Yes	8
66	46,XY,del(11)(q14-21)[9]/46,XY[1]	Yes	Yes	49+
72	47,XY,+8[11]	No	No	8
Poor risk				
39	46,XX,add(3)(q2?6)[4]/46,idem,-7[6]/46,XX[1]	Yes	No	18
39	42-45,XY,-3,-5,-7,+8,add(10)(p11-12),der(16)(q22),-17,der(17), t(7;17)(q11;q22-24)[cp10]	Yes	Yes	7
45	44,XY,-3,-5,-6,del(7)(q2?2),+8,?t(9;9)(p?;p?),-13,-15,del(20)(q1?1),+mar1,+mar2,inc[cp3]	Yes	No	2
53	42-44,der(1),der(3),der(7),der(16),der(19),inc[7]	Yes	No	4
57	46,XX,del(5)(q12q31)[2]/44-46,idem,add(1)(q?),-3,add(7)(q?),add(16)(q?), -17,+mar,inc[]/46,XX[]	Yes	No	0
61	44,XY,der(1)t(1;?16)(p1?;?q10),+del(1)(q1?),del(3)(q2?3q2?6), del(5)(q31q3?5),-7,-16,?del(20)(p1?3)[9]	Yes	No	0
64	46-54,XY,del(1)(q?),+4,-5,+?6x2,+8,+t(11;?22)(?q10;?q10)x2,-16,-17, t(17;22)(p?10;q?),+19,+idic(22)(q13)x2[cp5]/46,XY[2]	Yes	No	15
64	45,XX,add(1)(q?42),del(1)(q?32),der(5),der(7),del(7)(p22p15)inv(7)(p15q22),-19[13]	Yes	No	0
68	46-47,XY,-1,dic(5;7)(q14;q32),der(17)?t(1;17)(p22;q24),add(18)(q2?3),add(19)(p1?),?idic(21)(p1?)?add(22)(p11),+2~4mar[cp5]	Yes	Yes	5+
69	44-45,t(1;17)(q?;q?),der(1),add(3)(p?),der(5),add(16)(p?),inc[20]/46,XY[4]	Yes	No	0
72	40-46,X,der(3)?t(2;3),-5,-5,del(6)(q?),-7,add(18)(q2?),-20,inc[cp9]/46,XX[1]	No	No	7
84	68-75,XXX,-1,del(1)(p3),del(2)(p?),+del(2)(p?),+3,add(3)(q?),del(6)(q2),+del(6)(q2),add(11)(q23),+?dup(11)(q13q24),+6mar[cp14]/46XX[4]	No	No	0

CR, complete remission.

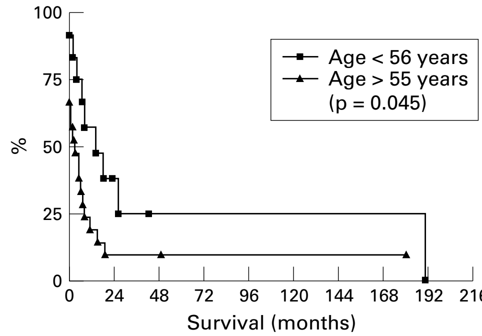

Figure 1 Overall survival by age.

older patients treated intensively was three months, with median EFS of zero months.

The remaining 11 patients were treated supportively with transfusion support or single agent chemotherapy to control the peripheral blast count. Median overall survival for these patients was also three months (range, 0–11).

There was a significant difference in overall survival between the two age groups, p = 0.045 (fig 1).

CYTOGENETIC ANALYSIS

Cytogenetic analysis was attempted in 27 patients. Seventeen patients had acquired karyotypic abnormalities. When categorised by MRC criteria, no patient had a karyotype classified as good risk. Table 2 shows the abnormal karyotypes.

Standard risk karyotype

Fifteen patients had a karyotype classified as standard risk, including eight patients with a normal karyotype. The child with Down's syndrome had trisomy 11 in addition to his constitutional trisomy 21. Analysis failed in three patients. The remaining patients had trisomy 8, loss of the long arm of chromosome 9, loss of the long arm of chromosome 11. The median age of these patients was 64 years (range, 3–80).

Ten patients from this group were treated with curative intent, with eight achieving CR (three were treated with DAT, two with ADE, one with FLAG, one with cytosine and mitoxantrone, and one with cytosine and idarubicin). Median EFS was six months (range, 0–180). Median overall survival was eight months (range, 0–205).

Poor risk karyotype

Twelve patients were classified as having a poor risk karyotype. The most frequent abnormalities were loss of chromosome 5 and loss of chromosome 7. The median age of this group was 63 years (range, 39–84).

Ten patients were treated with curative intent. Two patients achieved CR having received ADE and FLAG as induction treatment; however, both these remissions lasted only two months. Median EFS was zero months (range, 0–2) and median overall survival was three months (range, 0–18).

The difference in overall survival between these two groups was significant (p = 0.005) with no significant difference in age between the two groups (p = 0.44) (fig 2).

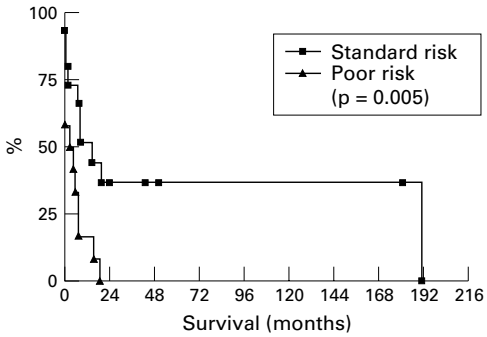

Figure 2 Overall survival by karyotype.

Discussion

This is the first demographic study of erythroleukaemia. As in previously published series, we have confirmed it to be an unusual form of AML, accounting for 3% of registered cases in our region. Although any age can be affected, it is six times more frequent in those 56 years and above. Patients typically present with anaemia and thrombocytopenia. Disease resistance is common and CR, if obtained, may be brief.

All but four cases had de novo AML, FAB type M6. It is not possible to determine whether our cases with pre-existing MDS had treatment induced erythroleukaemia or M6 transformation of incompletely eradicated MDS. In general, survival was poor with a low CR rate even in young patients treated intensively. The child with Down's syndrome behaved similarly to other reported cases.[12]

The MRC AML 10 trial contained data on 48 patients with M6 AML aged less than 56 years.[10] In that study, CR rates for patients with M6 AML were 84% and 89% for those treated with ADE and DAT, respectively, with overall survival at five years of 44% and 23%, respectively. There is no obvious explanation for the difference in outcome between our cases and those in the MRC report. However, the MRC study was not demographically based. It is certain that the M6 cases entered into it represent only a proportion of all nationally diagnosed cases. If the incidence of M6 AML is similar elsewhere within the UK, approximately 103 cases in patients aged less than 56 years would have presented within the UK during the course of the trial, approximately three times more than the total reported. Therefore, considerable selection bias affecting entry of patients with M6 into AML 10 cannot be ruled out. Further cytogenetic data on patients with M6 were not reported in the analysis of the MRC AML 10 trial.[6] Thus, it is possible that our demographic study contained a high proportion of patients with adverse cytogenetic features.

Other series have attempted to classify erythroleukaemia further by erythroblast morphology.[13–15] Despite some association between leftward shift of erythropoiesis and major karyotypic abnormalities such attempts have failed to predict survival or response to treatment. Other series have included cases not fitting the FAB criteria for M6 AML.[16]

We have confirmed the high prevalence of cytogenetic abnormalities reported by others. Davey *et al* reported an abnormal karyotype in 14 of 27 patients and Olopade *et al* found clonal abnormalities in 20 of 26 patients.[13 17] In both series, a high incidence of chromosome 5 and 7 abnormalities were noted, usually as part of complex karyotypic abnormalities.

The most striking findings of this demographic study, despite its relatively small size, are that karyotype at diagnosis predicted response to treatment and survival, and that overall outcome is substantially worse than in some published series of selected cases. It is not possible to make any deductions about the most appropriate therapeutic regimen. We believe it may be inappropriate to extrapolate the results of published studies of AML in general, and of M6 AML in particular, to older patients who comprise the great majority of patients with this disease. The outcome of M6 in older patients seems as dismal as for other elderly patients with AML.[18] Finally, although M6 AML remains a morphological identity there is a tentative suggestion from our results that at least in younger patients without Down's syndrome its outcome may be poorer than in other FAB defined categories of AML. However, further all inclusive demographic studies will be required to confirm this suspicion. Alternative means of treatment may emerge when data from various current studies of AML in the elderly are published.

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